09/720275

JC[?]ec'd PCT/PTO 21 DEC 2000

14839/US Hz/hr

Electrode arrangements for generating functional field barriers in microsystems

The invention relates to electrode arrangements for generating functional field barriers in microsystems adapted for manipulation of suspended particles, in particular functional microelectrodes for dielectrophoretic deflection of microscopic particles, and microsystems equipped with such electrode arrangements as well as their applications.

Manipulation of suspended particles in fluidic microsystems is generally known and has for example been described by G. Fuhr et al in "Naturwissenschaften", vol. 81, 1994, p. 528 ff. The microsystems form in particular channel structures through which a suspension fluid flows with the particles to be manipulated. As a rule the cross-sectional area of these channel structures is rectangular, with the width of the channel walls, which in operating position form the top and bottom (bottom/cover surfaces), being greater than the lateral channel walls (lateral surfaces). In the channel structures, microelectrodes are affixed to the channel walls, with high-frequency electrical fields being applied to said microelectrodes. Under the influence of the high-frequency electrical fields, based on negative or positive dielectrophoresis, polarisation forces are generated in the suspended particles, said polarisation forces making possible repulsion from the electrodes and, acting in combination with flow forces in the suspension liquid, making possible manipulation of the particles in the channel. As a rule, the microelectrodes of conventional microsystems are applied as straight electrode bands to the wider channel walls.

To generate the high-frequency electrical fields effective for dielectrophoresis, in each instance two electrode bands act in combination, said electrode bands being located at

opposite channel walls, both with the same shape and alignment. For example the straight electrode bands are aligned parallel to the alignment of the channel i.e. the direction of flow of the suspension liquid in the respective channel section or at a predetermined angle transversely to the alignment of the channel. For an effective and safe formation of polarisation forces at the particles, the length of the electrode bands exceeds the characteristic dimensions of the particles to be manipulated many times over (by a factor of approx. 20 to 50).

Conventional microsystems have disadvantages in relation to the effectiveness of generating polarisation forces; the stability and longevity of the microelectrodes; and a limited ability of generating force gradients within the channel structure. These disadvantages are in particular linked to the electrode bands which are formed along comparatively long lengths in the channel. The longer an electrode band, the longer a particle flowing past is in the sphere of influence of the electrode band. Consequently, the effectiveness of the respective microelectrode or the field barrier generated by said microelectrode, increases. However, long electrode bands are also more susceptible to malfunction. Faults in workmanship or mechanical loads can cause interruptions which lead to electrode failure. Furthermore, to achieve a force effect which remains constant along the length of the channel, and thus a reproducible force effect, microelectrodes have so far been limited to the above-mentioned straight electrode shape.

Due to the disadvantages mentioned, the application of said fluidic microsystems with dielectrophoretic particle manipulation has been limited to guiding the particles in the channel structure or to deflecting particles from a given flow.

It is the object of the invention to provide improved microsystems for dielectrophoretic particle deflection, with said arrangements being suitable to overcome the disadvantages of conventional microsystems, and in particular providing enlarged applications and making it possible to generate field barriers which are also effective in covering shorter channel sections. Furthermore it is the object of the invention to provide novel applications for such microsystems.

This object is solved by a microsystem with the characteristics according to claim 1. Advantageous embodiments and applications of the invention result from the dependent claims.

A microsystem according to the invention is in particular adapted to create field barriers in the microsystem along predetermined reference surfaces, said field barriers extending at least partly beyond the width of a channel in the microsystem, and comprising predetermined curvatures relative to the longitudinal extension of the channel, to the direction of flow of the suspension liquid in the channel or to the direction of movement of the (non-deflected) particles. In this context the term „reference surface" not only describes a two-dimensional formation but also a spatial region to which the field effect of the respective microelectrodes extends and in which the field barrier for dielectric influencing of the microscopic particles in the microsystem is formed. This spatial region essentially corresponds to a region through which the field lines of the effective microelectrodes pass; in the case of microelectrode pairs acting in combination, said spatial region essentially passes as a curved hypersurface between the microelectrodes, while in the case of individually acting microelectrodes it acts as a hypersurface encompassing the field line distribution of the

individually acting microelectrode. Reference surfaces define the locations where polarisation forces in the microscopic particles can effectively be generated. The microelectrodes are designed such that the reference surfaces, depending on the desired function of the respective microelectrodes, have a predetermined curvature in relation to the direction of movement of the particles in the microsystem, so that an optimal combined effect of the polarisation forces and of the mechanical forces is achieved. Therefore the field barriers are also referred to as functional field barriers. The term „curvature" used here does not refer to the curvature of field lines on straight microelectrodes as a result of the field lines exiting into the adjacent space. But rather, „curvature" refers to the shape of the field barriers formed on microelectrodes.

Preferably, the field barriers with the reference surfaces curved according to the invention are formed according to one of the following three basic forms. According to a first variant, an electrode arrangement according to the invention comprises at least one band-shaped, curved microelectrode extending on the wider channel wall (bottom surface and/or cover surface), at least partly across the channel width. In a second variant, at least one microelectrode is provided which is affixed to the narrower channel wall (lateral surface). In the third variant, at least one microelectrode is affixed to the bottom surface and/or the cover surface of the channel and at least one auxiliary electrode is affixed at a distance from the bottom surface or lateral surface of the channel. The auxiliary electrode supplies a deformation of the field lines emanating from the microelectrode or from the microelectrodes at the bottom surfaces or the side surfaces of the channel so that the reference surfaces curved according to the invention, are formed. In all the variants, the respective electrodes (microelectrodes,

auxiliary electrodes) per se can be band-shaped or point-shaped or area-shaped. The electrode arrangements of the second and third variant are also referred to as three-dimensional electrode arrangements, because microelectrodes are used which protrude from the planes of the bottom surfaces or lateral surfaces of the channel or which are arranged at a distance from said surfaces.

It is thus a subject of the invention, to optimise microelectrodes in relation to their effect on suspended particles which may comprise natural or synthetic particles, e.g. for generating maximum forces while at the same time causing minimum electrical losses.

The invention provides the following advantages. The design of the microelectrodes can e.g. be adapted to the flow profile in the suspension liquid. This provides the advantage that the microelectrodes can be shorter and can be designed for generating lesser barriers while being equally as effective as conventional microelectrodes in the shape of straight bands. This has an advantageous effect on the lifetime and function of the microelectrodes and thus of the entire microsystems. Moreover the space available in a microsystem can be used more effectively. Furthermore, electrode arrangements are provided with which gradients can be generated, and thus depending on the respective channel region, forces of various strength can be generated. It is for example provided for the field barriers of the microelectrodes to be designed such that larger polarisation forces act upon the particles in the middle of the channel when compared to the particles at the edge of the channel.

The creation of field barriers according to the invention along curved reference surfaces also makes it possible to create novel applications of microsystems, in particular for guiding suspended particles into particular channel

regions, for sorting suspended particles according to their passive electrical properties or for collecting or retaining suspended particles in particular channel sections. For this latter application, the microelectrodes are designed so as to comprise a geometric shape for retaining particles in a solution flow or for generating a particle formation. All the applications mentioned provide contactless manipulation of the suspended particles vis-à-vis the microsystem, a feature which is significant in particular for manipulating biological cells or cell components.

Preferred applications are in the field of microsystem technology for separation, manipulation, loading, fusion, permeation, pair formation and aggregate formation of microscopic small particles.

According to a particular embodiment of the invention, particle movement takes place in a microsystem with conventional electrode shapes or electrode shapes according to the invention, under the influence of centrifugal forces and/or gravitational forces.

Further details and advantages of the invention are provided in the drawings which are described below. The following are shown:

Figs. 1a to 1d: diagrammatic perspective views of a channel structure with microelectrodes for generating field barriers in a microchannel and examples of reference surfaces curved according to the invention;

Fig. 2: a diagrammatic top view of band-shaped curved microelectrodes;

Fig. 3:	a diagrammatic top view of a modified design of band-shaped curved microelectrodes;
Figs. 4a to 4c:	diagrammatic views for illustrating sorting electrodes for particle sorting;
Figs. 5a and 5b:	diagrammatic views of microelectrodes for generating field gradients;
Figs. 6a to 6e:	diagrammatic views of band-shaped collecting electrodes according to the invention;
Figs. 7a to 7c:	further embodiments of collecting electrodes according to the invention;
Fig. 8	a top view of various electrode arrangements for generating curved field barriers;
Fig. 9	a diagrammatic view of an electrode arrangement on the lateral walls of a channel;
Figs. 10 to 12:	various embodiments of three-dimensional electrode arrangements;
Fig. 13:	a diagrammatic top view of a segmented electrode arrangement; and
Figs 14 to 16:	further embodiments of the invention with a microsystem with centrifugal drive and/or gravitational drive of particle movement.

Fig. 1a diagrammatically shows an example of an embodiment of microelectrodes for generating field barriers in microchannels. The fluidic microsystem 20 is shown in sections in distorted perspective lateral view of a channel structure. The channel 21 is formed by two spacers 23 arranged at a distance on a substrate 22, spacers 23 supporting a cover part 24. The width and height of the channel is approx. 200 µm and 40 µm respectively but they can also be less. Such structures are for example made using process techniques of semiconductor technology which are known per se. The substrate 22 forms the bottom surface 21a of the channel 21. Accordingly the cover surface 21b (for reasons of clarity not specially emphasised) is formed by the cover part 24. The electrode arrangement 10 comprises microelectrodes 11, 12 attached to the bottom surface 21a or the cover surface 21b. Each of the microelectrodes 11, 12 comprises curved electrode bands which are described in more detail below.

In Fig. 1a the electrode bands form an electrode structure which is explained in detail below, with reference to Fig. 2. The other embodiments, described below, of electrode arrangement according to the invention, can be affixed to the bottom, cover and/or lateral surfaces of the channel 21. A suspension liquid flows through the microchannel 21 (from left to right in the illustration), with particles 30 being suspended in said suspension liquid. For example, it is the task of the electrode arrangement 10 shown in Fig. 1a, to lead the particles 30 from various tracks of movement within the channel to a middle track of movement according to arrow A. To this effect electrical potential is applied to the microelectrodes 11, 12 such that electrical field barriers are generated in the channel which force the particles flowing from the right, to move to the middle of the channel (direction of arrows B).

Typical dimensions of the microelectrodes 11, 12 are 0.1 to some tens of micrometers (typically 5 ... 10 µm) in width, 100 nm to a few micrometers (typically 200 nm) in thickness, and up to several hundred micrometers in length. Due to the small thickness of the electrodes, the interior of the channel 21 is not restricted by the top and bottom of the parts 23, 24 of the electrodes processed. Part 23 is a spacer whose structure forms the lateral channel walls.

The microelectrodes 11, 12 are selected by means of high-frequency electrical signals (typically at a frequency in the MHz range and at an amplitude in the volt range). The respective opposite electrodes 11a, 11b form a control pair although also the electrodes aligned in one plane can combine the effect of their selection action (phase, frequency, amplitude). The electrical high-frequency field generated through the channel 21, i.e. perpendicular to the direction of flow, acts in a polarising way on the suspended particles 30 (which can also be living cells or viruses). At the frequencies mentioned and with suitable conductivity of the suspension liquid surrounding the particles, the particles are repulsed by the electrodes. In this way the hydrodynamically open channel 21 can be structured via the electrical fields with a switch-on and switch-off action, or compartmentalised, or the tracks of movement of the particles in the passive flow field can be influenced. Furthermore, it is possible, despite the permanent flow, to slow down the particles or to position them on station without touching a surface. The type and implementation of the electrode arrangement formed for this purpose also forms part of the invention.

Below, different forms of electrode arrangements according to the invention are described. For reasons of clarity, Figures 2 to 13 may only show a planar electrode arrangement (or parts thereof), e.g. on the bottom surface of the channel.

Figs. 1b to 1c show the basic forms of field barriers or electromagnetic limitations which are implemented with electrode arrangements according to the invention corresponding to the above-mentioned variants. The illustrations are schematic diagrams of the reference surfaces on which the field barriers are formed with microelectrodes according to the invention. For the sake of clarity, only parts of the lateral surface (spacers 23) and of the bottom surface 21a of the channel, the microelectrodes 11, 12 and the shape of the reference surfaces (hatched), are shown.

According to the above-mentioned first variant, the field barrier in the channel is formed between two curved microelectrodes 11, 12 on the bottom or cover surfaces of the channel (Fig. 1b). Accordingly, the reference surface of the field barrier (shown hatched) is a curved surface positioned vertically against the bottom and cover surfaces. If the microelectrodes 11, 12 are for example curved according to a particular hyperbolic flow profile (see below), then the reference surface forms the cutout of the generated surface of a hyperbolic cylinder. If the microelectrodes 11, 12 are not arranged exactly on top of each other, then the reference surface is also oblique-angled in relation to the bottom and cover surfaces of the channel.

According to Fig. 1c, the reference surface, shown hatched, shows a spatial region impinged on by field lines extending from one microelectrode 11 at a lateral surface of the channel to a microelectrode 12 at the opposite lateral surface. In the example shown, the surface of the first microelectrode 11 is larger than that of the second microelectrode 12 so that there is a field line concentration at microelectrode 12. Consequently, the polarisation forces acting from the field barrier on

suspended particles are larger near the second microelectrode 12 than near the first microelectrode 11 (see also Fig. 9).

Fig. 1d shows the above-mentioned third variant with a three-dimensional electrode arrangement. The microelectrodes 11, 12 are on the bottom or cover surfaces of the channel while the auxiliary electrode 13 with a suitable confinement is arranged in the middle of the channel (see also Fig. 10). As a result of the auxiliary electrode 13, the field lines between the microelectrodes 11, 12 are distorted, resulting in the curved reference surface, shown hatched (shown in part only).

The illustrated reference surfaces only represent the positions of the field barriers without illustrating the forces acting in the respective regions, i.e. the height of the field barriers. Essentially the acting forces depend on the density of the field lines and the passive electrical characteristics of the particles to be manipulated in the respective channel region. The functional field barriers according to the invention are thus influenced by the geometric shape of the microelectrodes which combine their effect, both in relation to their shape (curvatures etc.) because the dielectrophoretic repulsion forces are essentially positioned perpendicular to the reference surfaces, and in relation to their areas (field line density).

Fig. 2 shows an electrode arrangement 10 according to the invention according to the above-mentioned first variant. Microelectrodes 11a, 11b are arranged on the bottom surface 21a of the channel of a microsystem, said channel being laterally delimited by the spacers 23. High-frequency electrical potential is applied to the microelectrodes 11a, 11b via the control lines 14; said microelectrodes 11a, 11b

act in combination to form a so-called particle funnel as follows.

The electrode arrangement 10 is intended to touchlessly focus, onto the middle line of the channel, the particles 30a flowing along the entire width of the channel or the entire volume, as is shown by the position of particle 30b. This arrangement has the advantage of optimising the electrode bands in relation to ensuring deflection (focussing) of the suspended particles, a shortening of the electrode arrangement in longitudinal direction of the channel and a reduction in electrical losses at the microelectrodes.

In this embodiment of the invention, the basic idea of the design of the microelectrodes consists of adapting the curvature of the reference surfaces formed by the field barrier, to the flow forces in the channel. For in microsystems with channel dimensions below 500 µm, due to the Reynolds number being low at these dimensions, laminar flows with predefined flow profiles form. The flow speed near the channel walls is lower than that in the middle of the channel (flow speed directly at the channel wall equals zero). As a result, the flow forces occurring near the channel walls are less than those in the middle of the channel. This makes it possible to manipulate the particles at the edge of the channel with lesser polarisation forces or with polarisation forces more steeply directed against the flow forces than in the middle of the channel. The combined effect of the flow forces and polarisation forces is explained below. If essentially the same polarisation forces are formed along the entire length of the microelectrodes, it is sufficient for safe deflection, for the particles to be manipulated, at the edge of the channel to encounter microelectrodes protruding more steeply into the channel than they do in the middle of the channel. This

makes it possible to achieve a significant shortening of the microelectrodes (see below).

In Fig. 2 the forces acting on the particles are illustrated as an example in individual sections of the microelectrode 11a. The respective total force is composed from the electrically-induced repulsion force F_P (polarisation force) and the driving force F_S which is exerted by the flow of the suspension liquid or from the exterior (e.g. in centrifugal systems as centrifugal force). The resulting total force F_R results from vector addition of forces F_P and F_S. If the vector of the total forces F_R does not intersect the field barrier of the microelectrode 11a, then a particle is safely deflected. The force diagrams in Fig. 2 illustrate that the driving force F_S increases towards the middle of the channel. To meet the above-mentioned condition of safe particle deflection, accordingly the angle between the alignment of the microelectrode 11a and the longitudinal direction of the channel changes from a steeper angle at the edge of the channel to a shallow angle (near-parallelity) in the middle of the channel.

Thus the microelectrodes 11a, 11b are curved depending on the flow profile. In the embodiment shown, each of the band-shaped microelectrodes consists of a multitude of straight electrode sections. But in a variation of this embodiment, a steady curvature can be provided. Corresponding to the parabolic or hyperbolic flow profile occurring in laminar flows, the curvature is also parabolic or hyperbolic.

According to the invention, the microelectrodes 11a, 11b form the field barriers along a curved reference surface.

The microelectrodes 11c, 11d are not provided for in practical application; in the illustration they serve the

purpose of comparing an arrangement according to the invention of polygonally curved microelectrodes with straight electrode bands providing the same deflection performance. It has been found that the microelectrodes 11a, 11b according to the invention are considerably shorter.

The narrow electrode bands shown in Fig. 2 are very sensitive to faults in workmanship and local interruptions. A hairline crack at the shoulder of a band-shaped microelectrode leads to failure of the entire microelectrode. This can be overcome by an electrode design as shown diagrammatically in Fig. 3. The structuring and covering technique described in relation to Fig. 3 can also be implemented with other embodiments of the invention.

Fig. 3 shows a microelectrode 11 with a control line 14. The electrode 11 consists of an electrically conductive layer 15 which carries an electrically non-conductive insulation layer or cover layer 16. The insulation layer 16 comprises structured recesses which expose the layer 15. In Fig. 3 the insulation layer 16 is shown hatched, while the (e.g. metallic) layer 15 is shown in black. Structuring of the insulation layer takes place according to the desired form of microelectrodes which in the example shown are arranged to form a particle funnel as shown in Fig. 2. The electrical field lines emanate from the metallic layer 15 into the channel only in the regions of the recesses, so that again field barriers with reference surfaces that are curved in an application-specific way are formed. This arrangement has the advantage that a small interruption of the exposed sections of the metallic layer 15 (i.e. of the microelectrode) does not lead to failure because the respective potential is also applied to the remaining metallic layer 15. For example the thickness of the layer 15 is approx. 50 nm to several µm, typically approx. 200 nm. The thickness of the insulation layer is around 100 nm

to several μm. Preferably the insulation layer comprises biocompatible materials (e.g. oxides, SiO_2, $SiNO_3$ and the like, polymers, tantalum compounds or the like).

Below, a further embodiment of the electrode arrangement 10 according to the above-mentioned first variant is explained with reference to Figs. 4a to 4c. An important application of fluidic microsystems consists of sorting the suspended particles depending on their passive electrical characteristics (hereafter referred to as polarisation characteristics during negative dielectrophoresis). Polarisation characteristics depend on the dielectric properties of the particles and their dimensions. The dielectric characteristics of biological cells are a sensitive indicator of certain cell characteristics or cell changes which per se could not be detected for example by monitoring cell size.

Sorting of particles depending on their passive electrical characteristics is based on the following principle. Whether or not a particle can pass the field barrier formed by a sorting electrode depends on whether or not the resulting force from driving force F_S and polarising force F_P (see above) intersects the field barrier. If the resulting total force F_R points through the field barrier, then the particle moves in this direction, i.e. the sorting electrode is passed. However if the resulting force F_R points to a region located upstream in relation to the sorting electrode, then the particle will move in this direction and will not be able to pass the sorting electrode. As explained above, the resulting force F_R depends on the flow speed in the channel and thus the x position of the particles. The flow speed increases towards the middle of the channel. Thus particles of relatively high polarisability which cannot pass the sorting electrode at the edge of the channel, are subjected to a stronger driving force F_S towards the middle of the channel, so that

they may then possibly move past the sorting electrode. The change in flow speed in x-direction follows the flow profile; as a rule it is non-linear. Accordingly, the use of a straight sorting electrode would result in non-linear separation behaviour. The implementation of curved field barriers according to the invention compensates for this. To this effect, microelectrodes 41a, 41b with a curvature depending on the flow profile are used according to the principles explained with reference to Fig. 2.

Fig. 4a shows two examples of curved microelectrodes 41a, 41b on the bottom surface 21a of a channel between lateral spacers 23. The flow in the channel is in y direction from left to right, with the arrows v showing the speed-flow profile in the channel. Upstream, in front of the actual sorting electrode 41a or 41b there is a straight microelectrode 47 whose task is to focus to a start line s, the particles 30 flowing in from the left. The microelectrode 47 can also be designated a focussing electrode. It can be a straight conventional deflector electrode (as shown) or a curved deflector electrode. Downstream of the focussing electrode 47, one of the sorting electrodes 41a or 41b is arranged whose task consists of leading the inflowing particles 30 into different tracks in x-direction in the channel, depending on their polarisation characteristics. Particles with a high polarisability 30a should move onward in different tracks in y-direction than particles with a low polarisability 30b.

The sorting electrode 41a is set up for linear force effect. For this purpose the curvature of the microelectrode is shaped according to the flow profile. If the flow speed is low, the setting angle between the microelectrode and the y-direction is steep; if the flow speed is high, the setting angle is more shallow. Thus the microelectrode 41a is S-shaped with a turning point in the

middle of the channel. After a particle has passed the sorting electrode 41a there is a linear relationship between the x-co-ordinate of the particle and its polarisability. If a non-linear sorting effect is intended, then the microelectrode can be curved like the sorting electrode 11b. The curvature is less pronounced than is the case with sorting electrode 11a so that the influence of the driving force F_S is not compensated for by the flow speed. Depending on the relationships set, a non-linear influence arises between the x-position of the particles and their polarisability after passing the sorting electrode 11b. This configuration can in particular be used to separate two particle types of different polarisability.

Results of experiments show that with a sorting arrangement according to Fig. 4a, it was possible to neatly separate erythrocytes from so-called Jurkart cells, although both cell types were of the same size.

If the flow profile in the channel is not distinctly parabolic in shape as shown in Fig. 4a, but instead is plateau shaped, then sorting electrodes 41c, 41d according to Fig. 4b are provided. The flow speed first increases from the direction of the edge of the channel before remaining essentially constant in the middle section of the channel. So as to achieve a linear sorting effect, the band shape of sorting electrode 41a is straight, while at its ends there are curvatures to take into account the changing driving force F_S. For a non-linear sorting effect, the sorting electrode 41d is curved. From the shoulder of the sorting electrode 41d at the control connection 14 to its end there is an increasing effect of the field barrier.

The shape of the sorting electrodes can also be adapted to more complicated flow profiles as is shown in Fig. 4c. In the microsystem 20 a first channel 211 with a high flow speed and a second channel 212 with a lesser flow speed

join to form a joint channel 21. Due to the laminarity of the flow, the flow profile at first remains intact also in the common flow path. Accordingly, the sorting electrodes 41e or 41f are curved so as to achieve a particular linear or non-linear sorting effect. The lower the flow speed, the higher the setting angle between the direction of the microelectrode (alignment of the reference surface) and the longitudinal direction of the channel (y-direction).

For reasons of clarity, the focussing electrode 17 according to Fig. 4a, is not shown in Figs. 4b and 4c.

The above-mentioned sorting takes place with the assumption that the potential is constant along the entire length of the microelectrode. In reality however, small electrical losses occur along the microelectrode so that the field barrier becomes progressively smaller from the shoulder of the microelectrode (at the control line) towards its end. This phenomenon can be taken into account in the curvature of the sorting electrodes in that at the side of the control line of the channel, a larger electrode curvature is provided than at the end of the sorting electrodes. But the phenomenon mentioned can also be purposefully used for additional non-linear separation effects. By using modified embodiments, the loss of potential towards the end of the microelectrodes can be amplified especially as a result of measures for forming field gradients. This means that the height of the field barrier formed by the microelectrode increases or decreases along the curved electrode band. Such gradient electrodes can be designed in a shape according to Fig. 5.

For particle sorting in relation to various groups of characteristics, several sorting electrodes according to Fig. 4 can be arranged in sequence in the direction of the channel. A characteristic potential or potential gradient at a predetermined frequency is applied to each sorting

electrode. For example relatively low frequencies (in the region of approx. 10 kHz) can be used for sorting in relation to various dielectric membrane characteristics, and high frequencies (above 100 kHz) can be used for sorting depending on the cytoplasmatic conductivity of biological cells.

Fig. 5 shows gradient electrodes 51a, 51b; for the sake of clarity, the electrode bands are straight. To set field barriers according to the invention, with curved surfaces, the gradient electrodes shown additionally comprise a characteristic application-specific curvature according to the principles explained above.

The gradient electrode 51a is formed by a closed electrode band around a triangular surface. As the distance from the control line 14 increases, the field line density is reduced in line with the fanning out of the triangle. The same applies to the gradient electrode 51b with two diverging partial bands 511b and 512b.

The collection and at least temporary arrangement of particles or particle groups in the channel through which suspension liquid flows, is a further important application of fluidic microsystems. To this effect, electrode arrangements according to the invention are shaped as collecting electrodes as is explained below with reference to Figs. 6 to 8.

Fig. 6a shows the basic shape of a collecting electrode. Again, only one microelectrode on the bottom or cover surface of a channel is shown, which acts in combination with that of a second microelectrode located at the opposite side of the channel. A collecting electrode 61a comprises an electrode band with an angle section 611a and a supply section 612a. The angle section 611a forms an angle pointing in the direction of flow (x-direction). The

opening angle of the angle section 611a is selected depending on the shape of the particles to be collected; preferably the opening angle is less than 90°, e.g. ranging from 20 to 60°. The opposing angle sections of electrodes whose effect is combined, form a barrier which the particles 30 to be collected cannot pass despite the driving force of the flow. This barrier is maintained as long as the collecting electrodes remain selected. The supply section 612a is electrically ineffective as a result of an insulation layer 16. Fig. 6b shows a modified embodiment of a collecting electrode 61b which is made with reference to the cover technique explained above with reference to Fig. 3. The electrically effective angle section 611b is formed by a recess in the insulation layer 16 as a result of which a deeper metallic layer 15 is exposed towards the suspension liquid containing the particles.

Figs. 6c and 6d show corresponding collecting electrodes 61c and 61d, each comprising a multitude of angle sections 611c or 611d. These angle sections are again set to collect inflowing particles 30. By adjoining the angle sections 611c or 611d across the longitudinal direction (x-direction) of the channel, the particles flowing in in the various channel sections can be collected selectively. A collecting electrode 61c or 61d is advantageously combined with one of the sorting electrodes according to Figs. 4a to 4c. The sorted particles are separately collected in the individual collection regions of the collection electrodes. The collection electrode 61d essentially corresponds to the collection electrode 61c. This completes implementation of the entire cover technique.

The collection electrodes 61c or 61d are particularly well suited to line up particles in the suspension flow in the manner of a start line from which the particles flow onward

simultaneously when the control potential of the collection electrodes is switched off.

Fig. 6e shows a further embodiment of a collection electrode 61e where a multitude of angle sections 611e is also provided, but with the angle sections being designed for collecting or gathering particles of various sizes or various sized accumulations of such particles.

Fig. 7a shows the accumulation of a particle group 300 using a collecting electrode 71a. This embodiment of a collecting electrode differs from the collecting electrode according to Fig. 6a only in its dimensions. This design is particularly well suited to the formation of particle aggregates. Again, preferably a combination with a sorting arrangement according to Figs. 4a to 4c is implemented.

The electrode arrangement according to Fig. 7b is configured for separate collection of particles or particle groups from the suspension flow in the channel which differ in relation to their flow track in x-direction. The microelectrode arrangement 71b comprises several partial collection electrodes each with an angle section 711b, whereby each partial collection electrode can be selected separately. When combining such a collecting electrode arrangement with a sorting arrangement according to Figs. 4a to 4c, the following method can be implemented with particular advantage.

First a particle mixture which flows through the channel in the microsystem is sorted depending on the passive electrical characteristics of the particles, and in this way is guided to various tracks mutually spaced apart in x-direction. Then in a collection electrode according to Fig. 7b, particle-type specific collection of the particles flowing in in the individual tracks takes place. By releasing the partial collection electrodes according to a

time sequence (in each instance by switching off the control potential), the previously sorted particles can flow on in groups in the microsystem. Downstream, the channel can for example be split into several sub-channels, with the groups of particle types specifically being directed to said sub-channels.

Fig. 7c shows a further collecting electrode 71c for generating a predetermined particle formation.

Depending on the application, the angle sections of the collecting electrodes shown in Figs. 6 and 7 can extend across the entire width of the channel or only across parts of the channel. Within an electrode arrangement, collecting electrodes can be provided for individual particles and/or for particle groups.

Further embodiments of combined sorting electrodes and collection electrodes are shown in Fig. 8 in top view of the bottom surface 21a of a channel delimited by spacers 23. The suspension liquid with suspended particles flows through the channel in y-direction. According to Fig. ~~8a~~ 8 an area-shaped microelectrode 81a on the bottom surface 21a and a straight band-shaped microelectrode 82a (shown by a dashed line) on the opposite surface of the channel, act in combination. The planar-shaped microelectrode 81a has been produced using the cover technique explained above. A metallic layer supports an insulation layer 86 with a recess according to the shape of the microelectrode 81a (drawn in black). The field lines between the microelectrodes 81a and 82a are inhomogenously aligned across the direction of flow, resulting in an asymmetric field barrier or again a reference surface which is curved according to the invention. In the middle of the channel the field line density is largest so that the electrically generated forces are located in the region of the highest flow speed. In this way an essentially constant balance

between the driving force resulting from the flow and the electrical polarisation force is formed in x-direction across the width of the channel. According to Fig. 8b, again a field barrier with a curved reference surface is formed. The microelectrodes 81b, 82b are both designed so as to be linear or band-shaped, they are not arranged in opposite positions but instead offset in relation to each other.

Fig. 8c shows an electrode arrangement for forming particle aggregates. The microelectrodes 81c, 82c form a number of funnel-shaped particle collectors arranged side by side. Each particle collector 11 is formed by a field barrier which in the direction of the flow of liquid first narrows in the form of a funnel before discharging into a straight channel section 812. The channel section is dimensioned such that two particles can be arranged one behind the other in the direction of flow. Due to the formation of adhesion forces, the particles form an aggregate (so called pair-loading in the direction of flow). The embodiment according to Fig. 8d is a modified version in that pair-loading takes place across the direction of flow. The individual collector elements 811d comprise electrode tips 813d on the inlet side. With these electrode tips 813d an additional barrier effect or filter effect can be achieved, and already existing aggregates or larger particles 30d can be precluded from assembling in the collecting electrode 81d.

Fig. 9 shows a further embodiment of an electrode arrangement according to the above-mentioned second variant. In the microsystem 20, a channel 21 is formed between the spacers 23; said channel is divided into sub-channels 211 and 212 by a separation wall 231. The separation wall 231 comprises an aperture 232 in the region of which the microelectrodes 91 and 92 are fixed to the lateral surfaces of the channel 21.

The microelectrodes 91 and 92 are so-called three-dimensional or high electrodes which at the lateral surfaces protrude from the planes of the bottom and cover surfaces of the channel 21. Manufacture of the microelectrodes 91 and 92 takes place using semiconductor processing technologies which are known per se (e.g. with the LIGA process). The microelectrode 91 is planar-shaped. The field lines extend to the opposing microelectrode 92 which is designed so as to be band-shaped, thus forming a curved collection area with the reference surface illustrated in Fig. 1c.

If the microelectrodes 91, 92 are controlled with electrical high-frequency potential, the particles 30 are pushed through aperture 232 into the adjacent sub-channel by means of negative dielectrophoresis. Such particle deflection can again take place selectively depending on the passive electrical characteristics of the suspended particles. Particles with low polarisability remain in the initial channel, while particles with high polarisability are deflected to the adjacent channel.

In the design according to Fig. 9, it is not mandatory that the microelectrode 91 be wired-up. It can be floating or it can be left out entirely. In this latter case the microelectrode 92 acts as an antenna. The microelectrodes 91, 92 preferably span the entire height of the lateral surfaces of the channel.

Fig. 10 (corresponding to Fig. 1d) shows an embodiment of an electrode arrangement according to the above-mentioned third variant. In a microsystem, again two sub-channels 211, 212 extend parallel to each other and separated from each other by a separation wall 231 comprising an aperture 232. The electrode arrangement according to the invention comprises microelectrodes on the bottom surfaces and cover

surfaces in the form of focussing electrodes 101, 102 and the auxiliary electrode 103. The auxiliary electrode is arranged at the separation wall 231, adjacent to the aperture 232, on the downstream side of the aperture 232. The auxiliary electrode 103 does not comprise a control line. It merely serves to form the reference surface of the field barriers formed by the electrode arrangement. The effect of the microelectrodes is combined as follows.

Focussing electrodes 101 and 102 are used to focus the particles 30a, 30b, flowing in in the sub-channels 211 or 212, to a middle line according to the position of the aperture 232 in the separation wall 231. Analogous to the deflection principle explained with reference to Fig. 9, the particles are deflected by the field barrier between the focussing electrode 101 and the auxiliary electrode 103 or between the focussing electrode 102 and the auxiliary electrode 103, through the aperture 232, into the adjacent sub-channel or they are left in the respective sub-channel. According to a preferred method, the focussing electrodes 101, 102 are operated at various frequencies so as to act in a particle-selective manner. Accordingly, again selective particle sorting into the sub-channels, or deflection of predetermined particles to an adjacent sub-channel can be achieved to carry out a particular treatment of the active ingredient with the respective suspension liquid provided in said sub-channel.

Fig. 11 shows a further three-dimensional electrode arrangement. A suspension liquid flows in y-direction in a channel 21. On the bottom surface 21a a group of microelectrodes 111 is arranged which protrude into the channel 21 and, spaced apart from each other, are aligned in the direction of flow (y-direction). Each microelectrode 111 is of cuboid shape. The microelectrodes 111 are made of metal or have a metallic surface coating without themselves comprising a control line.

On the opposite channel wall (cover surface, not shown) a planar-shaped electrode arrangement 112 (deflector electrode) is provided which acts in combination with the microelectrodes 111 as follows. The particles 30a flowing in y-direction are exposed to the field barriers which are asymmetrical due to the field-forming microelectrodes 111 and the field barriers are characterised by curved reference surfaces. Again, deflection of the particles takes place depending on the passive electrical characteristics. Weekly polarisable particles 31a flow on in y-direction while more strongly polarisable particles 30b are deflected into the spaces between the field-forming electrodes 111. The deflected particles 30b are correspondingly collected or gathered and are no longer conveyed onwards in the flow in y-direction.

According to a preferred embodiment the electrode arrangement according to Fig. 11 is provided at an intersection of two channels. The channel 21 directed in y-direction is intersected by a channel (not shown) through which a suspension liquid flows in x-direction (arrows A). This lateral additional flow continuously conveys the deflected particles 30b from the interspaces between the field-forming electrodes 111, into the cross-channel.

The geometry of the field-forming microelectrodes 111 can be adapted to the flow conditions and the field shape in the electrode interspaces and the shape of the opposite electrode arrangement 112.

The embodiment according to Fig. 11 can be modified by providing a volume-shaped field-forming electrode 121 instead of the field-forming electrodes 111 according to Fig. 12. The volume-shaped microelectrode is also referred to as a collection electrode 121. The collection electrode 121 is for example located at the bottom surface of a

channel (not shown); it comprises a cuboid block made of metal or a metal-coated material with a multitude of bore holes or reservoirs 121a arranged in columns and rows. The collection electrode is shown in sectional view at the front so that the reservoirs 121a can be seen. The collection electrode 121a 121 acts in combination with the area-shaped electrode arrangement 122 (deflector electrode) at the opposite channel wall as follows. Between the microelectrodes 122, 121, an asymmetric field barrier is generated which is configured to selectively deflect particles into the reservoirs 121a. The particles 30 flow in y-direction through the channel. Particles which are deflected downward into the collection electrode 121 by the field effect, are conveyed to the reservoirs 121a where they are fixed. After all reservoirs 121a have been filled, selection of the electrode arrangement can take place such that the particles are simultaneously transferred from the reservoirs 121a into the flow and in this flow are conveyed onwards in particle formation or aggregate formation. To this effect, if need be a further area-shaped electrode arrangement (not shown) can be provided below the collection electrode 121, the design of said further electrode arrangement being essentially the same as that of the area-shaped electrode arrangement 122.

According to a particular aspect of the invention, the microelectrodes in the individual embodiments can be segmented per se. However, in this case each microelectrode comprises a number of electrode segments which are arranged according to the desired electrode function. Fig. 13 shows a particularly versatile microelectrode 131 as an array of a multitude of pixel-shaped electrode segments arranged matrix-like. The electrode segments are arranged across the entire width of the bottom surface 21a between the spacers 23 and can be selected individually. This makes it possible to form the desired curved field barriers in particular according to the above-mentioned first variant, depending

on the concrete application, in particular depending on the particles to be manipulated, the flow conditions and the task of the microsystem. In Fig. 13 the presently selected pixels are shown in black while the pixels which are not selected are shown in white. In this case the segmented microelectrode 131 assumes the function of a particle funnel according to Fig. 2 by means of which the particles 30 are focussed to the middle of the channel.

The pixel-shaped electrode segments make possible loss-minimising focussing, sorting or collecting of particles. Each electrode segment can be selected with its own potential value (voltage) or its own frequency. In this way any specified dielectric force field can be generated along the channel. For example the influence of the flow profile can be compensated for in that the pixels arranged across the longitudinal direction of the channel are selected with a voltage which corresponds to the square root of the profile of the flow speed.

The size of the electrode segments and spacings between the electrode segments are preferably smaller than the characteristic dimension of the particles to be manipulated, but they can also be larger.

All particle manipulation takes place contact-free, so that the microsystems according to the invention are particularly suitable for manipulating biological cells or cell components.

Figures 14 to 16 show a diagrammatic perspective view of a design according to the invention of a centrifuge with a microsystem; a diagrammatic top view of a microsystem according to the invention configured for particle separation; and a diagrammatic top view of a programmable loading microsystem according to a further embodiment of the invention.

The embodiments of the invention described in this part refer to a combination of a microsystem comprising a microelectrode arrangement for carrying out negative or positive dielectrophoresis (dielectrophoretic microsystem) comprising a swinging rotor centrifuge. Both the dielectrophoretic microsystem (apart from the channel structures capable of being closed off at least on one side) and the swinging rotor centrifuge are known per se. Consequently there is no need to discuss their technical details here. It must be emphasised that in this document the term „swinging rotor centrifuge" is to be interpreted in the widest sense in that any centrifuge comprising at least one rotor which can be hinged upright depending on the speed, is included, which rotor itself forms the microsystem and the associated control system; into which rotor the microsystem and the associated control are integrated; or onto which rotor the microsystem and the respective control system are superimposed.

The particles manipulated according to the invention can comprise synthetic particles or biological objects. The synthetic particles are for example membrane-surrounded formations such as liposomes or vesicles or so-called beads or also macromolecules. The biological objects comprise for example biological cells or components of such cells (e.g. cell organelles), bacteria or viruses. The particles can also be aggregates or agglomerations of such particles and/or objects. The invention is preferably implemented using cell-physiologically relevant or medically relevant fluids with conductivities below 5 Siemens/m.

Fig. 14 is a diagrammatic overview of a device according to the invention for illustrating the affixation of a dielectrophoretic system to a centrifuge device.

A usual or application-dependent modified rotor of a centrifuge with axis of rotation 11 comprises four receptacles 12 into which the following are inserted so as to fit snugly and to tolerate the speeds applied: a microsystem 15 and control electronics 13 for controlling the microsystem with high-frequency alternating signals of different phase positions and amplitudes. The control electronics are connected to the microsystem 15 via cable 14, connector or otherwise. Preferably, the energy supply to the control device is via an electrical connection (rotation contact) with the stationary laboratory system. The microsystem comprises an input depot 16, the size of which can vary depending on the application, said depot 16 prior to centrifugation being filled with a particle suspension or cell suspension. From the input depot 16, a channel structure (details of which are provided below), extends to the collecting zones 17a, 17b which form an end of the microsystem 15 which end is closed at least during centrifuging. This means that the end of the microsystem can either be permanently closed off, or during standstill of the device can be opened by way of respective connection elements, and can be connected to predetermined additional systems for transferring the samples. The microsystem 15 is arranged on the retainer 12 such that during operation of the centrifuge (rotor turning around the axis of rotation 11 at a rotation frequency of ω), the centrifugal forces acting on the microsystem 15 and the particles located in said microsystem, are directed in the reference direction from the input depot 18 towards the collecting zones 17a, 17b. The retainers 12 are attached to the rotor (not shown) so as to be hingeable. With the centrifuge at a standstill, the retainers 12 are essentially aligned vertically or at a shallow angle in relation to the axis of rotation. During operation of the centrifuge, depending on the speed, the retainers 12 come up to a larger angle until they are aligned horizontally, i.e. perpendicular to the axis of rotation 11. Under the influence of gravity (with the

centrifuge at a standstill) or the centrifugal forces, the particles flow through the electronically controlled microchannel system and congregate in the collection zones (e.g. at the closed end of the part of the microsystem pointing away from the rotor axis).

During this passage, the particles are treated according to predetermined programs (see below). Since the particles carry out various movements and assume various end positions depending on their density, the present invention combines the advantage of centrifugal separation and centrifugal movement with the possibilities of pre-programmable dielectrophoresis. Normally, negative dielectrophoresis of the particles is used; in exceptional cases also positive dielectrophoresis. Control of particle movement via rotational speed (ω) of the rotor 11 is a further advantage provided by the invention. Since in this case it is also possible to pass through programmable variations, a second complex of determinable parameters during particle manipulation is provided.

The centrifuge device comprises a rotational speed control (not shown) which provides a reproducible and precise speed adjustment in particular at low speeds. The rotational speed is selected application-specifically, depending on the desired speed of the particles to be manipulated and depending on the actual design of the centrifuge. For biological particles (e.g. cells), the interesting particle speeds are below approx. 500 µm/s (preferably ranging from 50 to 100 µm/s); for synthetic particles (e.g. latex beads) the speeds are higher (e.g. some m/s). The rotational speed of the centrifuge is selected according to the interrelationship between rotary speed and centrifugal force, depending on the size or density of the particles. The following information refers to a spacing of the microsystem from the rotor axis, ranging from 1 to 10 cm. For particle diameters ranging from 50 to 600 nm (e.g.

viruses), rotational speeds can range from 1 to 1,000 rpm. In the case of particles with a diameter of approx. 5 µm, rotational speeds up to 100 rpm are preferred, but higher speeds can be set. In the case of particularly small particles, e.g. macromolecules, still higher rotational speeds can be realised. For biological cells, at a distance between the microsystem and the axis of rotation 11 of approx. 5 to 10 cm, speeds ranging from a few revolutions per minute to several hundred (e.g. 600) revolutions per minute result; preferably below 100 rpm. Achievable centrifugal forces are in the region of pN to nN. The centrifuge is however also designed for higher speeds which can be set in particular for small particles or for cleaning or rinsing purposes. These increased speeds can range up to the speeds of conventional laboratory centrifuges.

The rotational speed of the centrifuge is also selected depending on the dielectrophoretic forces acting on the particles in the microsystem. The dielectrophoretic forces as polarisation forces depend on the type and size of the particles. The speed is preferably selected so that the centrifugal forces acting on the particles are less than, or equal to, the dielectrophoretic forces. If these are not known, the speed can also be selected in relation to the following criterion. The particles must move slowly enough along the channel structure, so that sufficient time remains for dielectrophoretic deflection when they pass the microelectrode equipment. The effectiveness or ineffectiveness of dielectrophoretic deflection depending on rotational speed, can be acquired optically or electrically using suitable sensors.

Fig. 15 diagrammatically shows a microsystem for separating a particle mixture comprising larger particles 21 (e.g. cells) and smaller particles 22, present in a suspension. The centrifugal forces act in the direction of the arrow 23

(reference direction). Typical dimensions of the channel structure 24 are as follows:

Width: some 10 µm to some mm
(typically: 200 - 400 µm)
Length: some mm to some cm
(typically: 20 - 50 mm)
Height: some µm to some 100 µm
(typically: 50 µm)

On the top 25 and on the bottom 26 of the channel 24, microelectrodes 27a, 27b are arranged opposite each other. When these microelectrodes are selected with an alternative voltage (as a rule a frequency in the MHz range and an amplitude of some volts), they create field barriers across the channel. By way of negative dielectrophoresis (under certain circumstances also positive dielectrophoresis), said field barriers deflect the particles (the large particles in the case shown here).

The channel structure 24 extends from the input depot 28 to the closed ends 29a, 29b of the channel into which said channel, which is straight in the middle section, branches. A first pair of the microelectrodes 27a, 27b is arranged directly at the end of the input depot 28, which end faces the channel, so as to form a field barrier which protrudes transversely into the channel and which has the task of forcing the large particles 21 into the channel 24 shown on the right in top view. A second pair of the microelectrodes 27a, 27b is arranged directly in front of the branching-off to the ends 29a, 29b of the channel; it forms a field barrier which extends transversely across the width of the channel up to the branching-off leading to the channel end 29b, said field barrier being provided to guide the large particles 21 to this end of the channel.

A manipulation process according to the invention which in this example is directed to separate the particles, comprises the following steps.

Before centrifugation, the microsystem is filled with a suitable liquid. The microsystem has already been installed in a retainer 12 of the centrifuge (see Fig. 14). But installation can also take place after filling of the microsystem. Shortly before start of centrifugation, the electrodes 27a, 27b are controlled and in the input depot 28, the suspension of the particles to be separated is added, e.g. by means of a pipetting apparatus. At first, the centrifuge is in idle position, i.e. the microsystem is aligned so as to be vertical or at a slight inclination to vertical. Gravity acting on the particles results in the particles descending at different speeds to the channel structure (sedimentation), with the speed of descent depending on the density of the particles. Depending on the desired particle speed, further movement of the particles towards the ends of the channels is exclusively under the influence of gravity or under the combined influence of gravity and centrifugal forces. Centrifugation can thus be understood to be sedimentation under the influence of an artificially increased acceleration of fall. The moving particles are separated according to their size, by the electrical field of the first pair of microelectrodes.

Fig. 15 shows the conditions during sedimentation or centrifugation. As a result of the centrifugal forces being precisely adjustable via the rotational speed, the particles move to the lower part of the microsystem. According to the usual centrifugation principles, the particles with the highest density sediment first. Since the electrical field barrier in the channel moves the particles 21 to the right, while particles 22 are not influenced by this process, separation of the two particle types into the ends of the channels 29a, 29b takes place.

In addition, the particles in each of the ends of the channels are arranged according to their density as is the case in conventional centrifugation. The microsystem shown can be regarded as a basic form of a device according to the invention. Depending on the application, this basic form can be enlarged, expanded or combined with further microstructures. It provides the advantage that there is no solution flow, while particle movement is nevertheless directed and adjustable. Such systems can also generate movement in the opposite direction if the particles are buoyant.

Starting with the base form shown, a microsystem according to the invention can be extended as desired, as is known per se from dielectrophoretic microsystems. Accordingly, the channel structure may in particular comprise several individual channels, interconnected by means of branch channels. Channels can be straight or curved. Curved channel shapes (e.g. arcs, meanders, curves, angles etc.) can in particular be used to investigate differences in binding between the particles and the channel walls.

According to a further modification, the microsystem can be attached to the retainer 12 (see Fig. 14) so as to be rotatable. During a first centrifugation process, e.g. particle separation according to Fig. 15 takes place in a first orientation of the microsystem. Subsequently, the orientation of the microsystem is changed by 180°, so that gravitational and/or centrifugal forces act in opposite direction to the direction of arrow 23. In this case the ends 29a, 29b of the channels assume the function of input depots from which further distribution of the separated particles into sub-groups or to treatment (loading with substances, electroporation and similar) can take place if suitable channel structures (additional lateral branch-channels) are present. Depending on the channel structure, changes in orientation other than the 180° reversal are

possible. Furthermore it is possible to design the retainer 12 such that the microsystem is rotated during centrifugation.

Fig. 16 shows a further embodiment of the invention, namely a programmable loading-microsystem for cells or particles. In this embodiment the centrifugation channel is divided into three parts 31a, 31b, 31c. In the intermediary walls there are apertures 32 through which again electrodes 33 protrude at the top and bottom of the channel. The apertures are matched to the particle size (typically 5 to 20 times larger than the diameter). At first, each of the parts 31a to 31c of the channel is filled with various solutions which are used for chemically changing or loading the particles. After this, the particles are inserted into one part of the channel (in the example shown e.g. 31c). Through centrifugation, the particles (e.g. first the black ones, then the light ones) move to the electrodes 33 where they can automatically be conveyed via the electrical field barriers to the adjacent solution through the apertures 32.

Here too, sorting into the three channel ends 31d, 31e, 31f and at the same time arrangement of the particles according to their mass density, take place.

The microsystems are further characterised in that they may comprise apertures (inflows, through-flows, outflows) which can be closed off so that after or before centrifugation, the particles can easily be removed or inserted. Furthermore, all the microelectrode elements (holding electrodes for particles, microfield cages etc.) can be installed which are known per se for dielectrophoretic influencing of particles, and which are used in conventional microsystems which operate with flowing liquids. Based on the combined action of gravitational or centrifugal forces with dielectrophoretic forces, the method according to the invention is an electrically

controlled or active centrifugation. Furthermore, combinations can be provided with the effect of optical forces (laser tweezers), magnetic forces (influence on magnetic particles), or mechanical forces in the form of ultrasonic forces.

Areas of application of the invention include in particular: cell separation / cell fractionation, cell sorting, cell loading (molecular, nano-particles, beads), cell discharge (molecular), cell permeation (so-called electroporation), cell fusion (so-called electrofusion), cell pair formation, and cell aggregate formation.

The invention is not limited to particular solution liquids or suspension liquids. It is advantageous if the viscosity of the liquid contained in the microsystem is known. If the viscosity is known, the rotational speed for setting a particular particle speed can be determined on the basis of tabular values or by means of a program algorithm. Alternatively, it is however also possible to acquire the actual speed of the particles in the microsystem during centrifugation (e.g. by using an optical sensor) and to regulate the rotational speed for setting a particular particle speed. It can be provided that in various sub-sections of the channel structures, e.g. in parallel channels which are interconnected only via an aperture, liquids of various viscosity are contained. In this case however, viscosities are preferred which ensure that diffusion of the liquids through the aperture is relatively low or negligible over the entire period of centrifugation.

If the mass density of the particles is less than that of the liquid in the microsystem, the invention can be implemented with corresponding modifications in that particles are introduced on the side of the microsystem away from the axis of rotation. They then move to the other

end of the microsystem under the influence of buoyancy or by the combined effect of buoyancy and centrifugal forces.

The microsystem is designed corresponding to the channel structure and alignment of the electrodes in dependence on the particular application. As a rule, the cross-sectional dimensions of channels are significantly larger than the diameter of individual particles. Advantageously, this prevents blocking of the channels. If only particles with particularly small dimensions have to be manipulated (e.g. bacteria or viruses or cell organelles), then the channel dimensions can be reduced accordingly, e.g. to dimensions below 10 μm.

The invention is implemented with a microsystem which is closed off at least on one side. The closed end can be a closed-off end of a channel, a closed-off collection zone or a closed-off hollow space in the microsystem. With particle manipulation according to the invention, there is essentially no movement of liquid towards the closed end. In particular with implementation of collection zones or hollow spaces at the closed-off end, this means that these, like the entire microsystem, are filled with the solution or suspension for the particles at the beginning of particle manipulation.

If during manipulation of the particles, agglomerations or temporary blockages of the channel structures occur, according to the invention it is provided to temporarily increase the rotational speed of the centrifuge so as to detach the adhering particles and move them on.